
ORIGINAL ARTICLE**Potential Association of Hypothyroidism and Cardiovascular Disorders among Type II Diabetes Mellitus Patients Visiting for Dental Treatment***Shantala Arunkumar^{1*}, Shyam Amur², Krishna M. Burde¹, Lijoy Abraham¹**¹Department of Oral Medicine and Radiology, ²Department of General Medicine, Sri Dharmasthala Manjunatheshwara College of Dental Sciences, Sattur, Dharwad-580009 (Karnataka) India*

Abstract:

Background: Diabetes is a group of etiologically different metabolic defects characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. **Aim and Objectives:** The study intended to estimate prevalence of hypothyroidism among Type 2 Diabetes Mellitus (T2DM) patients and to substantiate the association of these two disorders with cardiovascular diseases. **Material and Methods:** The study included 208 T2DM patients; all were evaluated for diabetes mellitus, hypothyroidism and cardiovascular disorders by history, clinical examination and investigations. They were divided as Diabetes Mellitus (DM) and Diabetes Mellitus Hypothyroidic (DMH) categories. DM category was further divided as: Diabetic (D) and Diabetic Cardiovascular (DC) groups, DMH category as Diabetic Hypothyroidic (DH) and Diabetic Hypothyroid Cardiovascular (DHC) groups. Intra and inter category comparison of biochemical and clinical parameters were done. **Results:** Out of 208 T2DM patients, DM category had 102 patients and DMH category 106 patients, On intracategory comparison of various biochemical parameters between the two categories, in DM category, Fasting Blood Sugar (FBS) ($p=0.00$), Postprandial Blood Sugar (PPBS) ($p=0.34$ and $p=0.02$), Low Density Lipoprotein (LDL) ($p=0.00$ and $p=0.20$) were significantly higher and High Density Lipoprotein (HDL) was lower in both D and DC groups, total cholesterol in DC ($p=0.23$) group was significantly higher and triglycerides were within normal. In DMH category, FBS ($p=0.01$ and $p=0.00$), serum Thyroid Stimulating Hormone (TSH) ($p=0.00$), LDL, total cholesterol ($p=0.00$), LDL ($p=0.02$ and

$p=0.00$) and triglycerides ($p=0.00$ and $p=0.01$) were significantly higher in both DH and DHC groups, the HDL was significantly lower in DHC group. There was no association between DM category with blood pressure and electrocardiogram parameters, but in DMH category there was significant association seen, as $p=0.02$ and $p=0.06$ respectively. On inter group comparison between DM and DMH categories for biochemical parameters, there was statistical significance was found with serum TSH ($p=0.00$), total cholesterol ($p=0.01$) and LDL ($p=0.007$), where as FBS, PPBS, triglycerides, HDL were not significant. **Conclusion:** Dental treatments are stress inducing, so cardiovascular events are more likely to occur hence complete evaluation by physician is mandatory.

Keywords: Type 2 Diabetes Mellitus, Hypothyroidism, Dyslipidemia, Cardiovascular Disorders

Introduction:

Diabetes is a group of etiologically different metabolic defects characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. The World Health Organization (WHO) has projected that the global prevalence of diabetes will rise to 300 million (7.8%) by 2030 [2]. India has already become the "Diabetes capital" of the world with over 3 crore affected patients [3]. Thyroid dysfunction manifests either as hyper or hypothyroidism and is reflected in the levels of T3, T4 and Thyroid Stimulating Hormone (TSH). Diabetes and thyroid diseases are two common endocrinopathies seen in the general

population, the association between diabetes and thyroid dysfunction was first published in 1979, after, which number of studies have estimated prevalence of thyroid dysfunction among Diabetes Mellitus (DM) patients ranging from 2.2-17%. However, a few studies have estimated higher prevalence of thyrodiabetics i.e. 31% and 46.5% respectively [4].

DM appears to influence thyroid function at two sites; first at the level of hypothalamic control of TSH release and second at peripheral tissue by converting T4 to T3. Abnormal thyroid hormone levels are commonly found in DM patients, the reason for this is thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism and excess or deficit of either one can result in functional derangement of the other. Reduced glucose absorption from gastrointestinal tract accompanied by prolonged peripheral glucose accumulation; gluconeogenesis, diminished hepatic glucose output and reduced disposal of glucose are hallmarks of hypothyroidism [5].

In Type 2 DM (T2DM) cardiovascular diseases are the most prevalent cause of morbidity and mortality, the association between hyperglycemia and intracellular metabolic changes can result in oxidative stress, low-grade inflammation, and endothelial dysfunction. Diabetic patients with poor metabolic control experience microvascular and macrovascular complications and concomitant dyslipidemia worsens cardiovascular risk due to the peculiar atherogenic profile composed of increased Very Low-Density Lipoprotein (VLDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol, triglycerides levels and decreased High Density Lipoprotein (HDL) cholesterol levels. With such lipoproteins modified by oxidation and glycosylation, there is a reduction on vascular compliance predisposing to early and aggressive atherosclerosis [6].

The dysregulation of autonomic nervous system in DM [Cardiovascular Autonomic Neuropathy (CAN)] is responsible for modulating the activity of the sinus node (heart rate), ventricles (end systolic and diastolic volume) and blood vessels (systemic vascular resistance), may contribute to the development of arterial stiffness, left ventricular hypertrophy, and diastolic dysfunction leading to resting tachycardia, postural hypotension, exercise intolerance, abnormal coronary vasomotor regulation (risk of silent myocardial ischemia and infarction) [7].

Thyroid and cardiovascular system are intimately linked and thyroid hormones modulate every component of the cardiovascular system necessary for normal development and function, even endothelial mediated vasorelaxation is partly dependent on thyroid hormone signaling. In chronic hypothyroid states there is increased risk of atherosclerosis often associated with dyslipidemia (hypercholesterolemia) and hypertension, less common are the restrictive cardiomyopathy, endocardial fibrosis, myxomatous valvular changes and pericardial effusion [7].

The coronary artery disease accompanying hypothyroidism may be preexistent or be aggravated by the thyroid dysfunction. The hypertension associated with hypothyroidism may be asymptomatic or attended by overt myocardial ischemia, including angina pectoris or myocardial infarction. When coronary artery disease is known or suspected to be present, treating hypothyroidism is a challenge for the clinician. So the present study was planned to assess the association of T2DM with hypothyroidism and the effect of these two co-morbidities on cardiovascular system in a dental set-up. Patients with DM and Hypothyroidism may have an undiagnosed cardiovascular disease which leads to complications during dental procedures.

Material and Methods:

The cross sectional observational study was conducted at the Outpatient Department (OPD) of general medicine in a dental institution under the guidance of physician and subjects included were patients suffering from diabetes and those who detected to have diabetes during the routine blood investigation for fitness to undergo dental treatment.

A total of 208 T2DM patients were recruited in the study, among which 125(60%) were old cases and were on medication. Eighty three (40%) were newly detected to have DM on routine blood investigations prior to undergo dental treatment.

All newly diagnosed cases were also evaluated for hypothyroidism and Cardiovascular Diseases (CVDs) by taking detailed history, clinical examination by measuring Blood Pressure (BP), Electrocardiogram (ECG) and lipid profile [Total cholesterol (TC), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and triglycerides] and serum Thyroid Stimulating Hormone (TSH) levels. All the blood investigations except Postprandial Blood Sugar (PPBS) were done under fasting condition by drawing the intravenous blood samples during morning time. The old DM cases were evaluated by referring to the patient's reports. Before enrollment, each patient consented to a predefined protocol and study procedure was approved by the local Ethics Committee.

After the history, clinical examination and investigations, 208 patients divided into two categories as DM and Diabetes Mellitus Hypothyroidic (DMH) categories.

In DM category, the patients suffering from diabetes and diabetes with associated CVDs and not suffering from hypothyroidism were included. This DM category again divided as Diabetic (D) and Diabetic Cardiovascular (DC) groups. In

Diabetic (D) group, there were patients suffering from diabetes without CVDs are included and in DC, where patients with diabetes with CVDs are included. In DMH category, the patients suffering from diabetes with associated CVDs and hypothyroidism were included. This DMH category again divided as Diabetic Hypothyroidic (DH) and Diabetic Hypothyroidic Cardiovascular (DHC) groups. In DH group, there were patients suffering from both types of diabetes with hypothyroidism and in DHC, where patients with diabetes, hypothyroidism and CVDs were included

Laboratory Data:

Morning time venous blood sample were collected in fasting condition, assessed for Fasting Blood Sugar (FBS), serum TSH, lipid profile and after 2 hours of breakfast for PPBS. For glucose estimation, Siemans – Dimention RxL Max, fully automated chemistry analyser and for total cholesterol, Siemans–Enzymatic Cholesterol Oxidase-Peroxidase Method (CHOD-PAP), HDL, LDL and Triglycerides by Enzymatic Colorimetry method. The serum TSH ADVIA centaur CP-two site sandwich immunoassay using Chemiluminescence Immunoassay (CLIA).

The following guidelines for diagnosis of hypothyroidism were considered:

- 1) Normal - when TSH < 5.5 μ IU/L was within the normal range
- 2) Primary hypothyroidism -when TSH > 5.5 μ IU/L.

For new cases the diagnosis of DM was based on the WHO criteria for T2DM: FBS \geq 126 mg/dl, PPBS \geq 200 mg/dl at 2 hours in the 75 g oral glucose tolerance test or symptoms of DM and Random Blood Glucose (RBS) > 200mg/dl was followed. For lipid profile TC- > 200mg/dl (normal range 150-200 mg/dl); LDL- > 130mg/dl (normal < 130 mg/dl) HDL- > 70mgs/dl (normal

range 35-70 mg/dl) and Triglycerides >150 (normal range 40-150 mg/dl) were considered as dyslipidemia

Statistical Analysis:

Collected data of each patient was evaluated for demographic details, diseases status for diabetes, hypothyroidism and associated CVDs by biochemical and clinical parameters and entered into Statistical Package for Social Sciences (SPSS 15.0 for windows) for analysis. The results were expressed as mean \pm SD of each variable. The comparison between means was performed by student t test. $P=0.05$ or less was interpreted as significant for the analysis, results were drawn are expressed in tables (Table 1, 2, 3, 4, 5, 6 and 7).

Results:

The number of T2DM patients each group with the duration of the disease is shown in table 1. In DM category there were 102 patients, out of which 47(22.60%) patients had only diabetes (D group) and 55(26.44%) patients had diabetes with associated cardiovascular diseases (DC group) with the mean duration of disease in years is 5.85 ± 4.69 and 6.94 ± 4.27 respectively. In DMH category, there were 106 patients, out of them 41(19.71%) patients were suffering from diabetes and hypothyroidism (DH) and 65(31.25%) patients had DM, hypothyroidism and cardiovascular diseases (DHC) with mean duration of the disease 5.15 ± 6.16 and 5.59 ± 4.25 .

Out of 208 patients, 124 patients were old cases suffering from DM with or without CVDs and or hypothyroidism, in this 67 patients had associated CVDs and hypothyroidism and only 58 patients did not have hypothyroidism but had CVDs. The 83 patients were newly detected diabetic cases on routine investigations before the dental treatment, 44 patients had DM with or without CVDs and 39 patients had DM with associated hypothyroidism

with or without CVDs (shown in Table 1). In this study we assessed the time of occurrence of hypothyroidism among DMH group, among 106 patients, 34(32.5%) patients had hypothyroidism first and 43(40.5%) patients had diabetes first and hypothyroidism later on, but 29(27.4%) patients detected to have both diabetes and hypothyroidism at the same time (shown in Table 2).

In table 3, sex and age distribution is shown, in DM category, there were 22 Males (M) and 20 Females (F) in the D group with the mean age range of 51.36 ± 9.08 and 52.73 ± 12.69 respectively and in DC group 30M and 25F with age range of 52.73 ± 11.80 and 50.19 ± 10.66 respectively. In DMH category, we observed strong female predominance, as there were 32F and 9M in DH group with mean age range of 55.38 ± 11.56 and 50.85 ± 9.78 respectively and in DHC group also 46F and 19M with age range of 56.8 ± 12.69 and 51.22 ± 10.14 respectively. In this we noticed that male patients in DMH category were at higher age (56.85 ± 12.69) range compared to females (50.19 ± 10.66 and 52.73 ± 12.6) of both the categories and males (51.36 ± 9.08) of DM category, so females are commonly affected at their early age in DMH category compared to DM category.

Table 4 shows intragroup comparison of various biochemical parameters of DM and DMH categories. In DM category, FBS ($p=0.00$), PPBS ($p=0.34$ and $p=0.02$), LDL ($p=0.00$ and $p=0.20$) were significantly higher and HDL is lower in both D and DC groups and total cholesterol in DC ($p=0.23$) group was significantly higher, whereas triglycerides were within normal range. In DMH category, FBS ($p=0.01$ and $p=0.00$) and serum TSH ($p=0.00$), LDL, TC ($p=0.00$), LDL ($p=0.02$ and $p=0.00$), triglycerides ($p=0.00$ and $p=0.01$) are statistically higher in both DH and DHC groups, the HDL significantly lower in patients in DHC group. There was no association between DM

category with blood pressure and ECG parameters as shown in Table 5, but with DMH category there was statistically significant association seen with ECG as well as BP as the $p=0.002$ and $p=0.006$ respectively. On inter group comparison between DM and DMH categories for biochemical

parameters, there was statistical significance was found with serum TSH ($p=0.00$), total cholesterol ($p=0.001$) and LDL ($p=0.007$), where as FBS, PPBS, triglycerides, HDL were not statistically significant, as shown in Table 6.

Table 1: Number of Patients and Duration of Diseases

Disease Categories	Disease Groups	Number of Patients	Duration of Diseases (Mean±SD)
DM (N=102)	D	47 (22.60%)	5.85 ±4.69
	DC	55 (26.44%)	6.94 ±4.27
DMH (N=106)	DH	41 (19.71%)	5.15 ±6.16
	DHC	65 (31.25%)	5.59 ±4.25

Table 2: Time of Occurrence of Disease

Disease Category	Diabetes First	Hypothyroidism First	Both at Same Time	Total Number of Patients
DMH	43 (40.5%)	34 (32.5%)	29 (27.4%)	106

Table 3: Sex and Age Distribution of Patients

Disease Category	Disease Groups	Sex		Age Distribution (Mean Age in Years)
		Male	Female	
DM	D (N=47)	Male	27	51.36 ± 9.08
		Female	20	52.73 ±12.69
	DC (N=55)	Male	30	52.73 ±11.80
		Female	25	50.19 ±10.66
DMH	DH (N=41)	Male	9	55.38 ±11.56
		Female	32	50.85 ±9.78
	DHC (N=65)	Male	19	56.85±12.69
		Female	46	51.22 ±10.14

DM - Diabetes Mellitus, DMH - Diabetes Mellitus Hyperthyroidism

D - Diabetic, DC - Diabetic Cardiovascular, DH - Diabetic Hyperthyroidism, DHC - Diabetic Hyperthyroidism Cardiovascular

Table 4: Intra Group Comparison of Various Biochemical Parameters within Diabetes Mellitus and Diabetic Hypothyroidism Categories

Biochemical Parameters		DM				DMH			
		D (N=47)	P Value	DC (N=55)	P Value	DH (N=41)	P Value	DHC (N=65)	P Value
Sugar	FBS	163.34 ±54.53	0	158.69±56.56	0	150.25±46.22	0.001	150.68± 52.23	0
	PPBS	233.40±73.63	0.034	233.01±81.84	0.002	211.02±52.24	0.125	220.48± 52.43	0.068
Thyroid	TSH	2.24±0.904	0.123	2.13±0.970	0.067	16.63±23.35	0	17.22± 24.82	0
Lipid Profile	TC	166.40±35.72	0.062	168.83±36.72	0.023	149.85±38.15	0	149.165±43.47	0
	HDL	39.30 ±7.57	0.001	41.56 ± 7.77	0.009	34.62 ±7.91	0.091	47.14 ± 44.31	0
	LDL	101.85±29.83	0	107.75±32.92	0.02	100.17±43.07	0.002	131.34± 38.41	0
	TGA	147.96±38.98	0.441	145.64±30.81	0.111	145.31±45.73	0	140.21 ± 32.4	0.001

Table 5: Clinical Parameters (Electrocardiogram and Blood Pressure)

Clinical Parameters		DM Category		DMH Category	
		D (N=47)	DC (N=55)	DH (N=41)	DHC (N=65)
ECG	Normal	46	32	34	35
	Abnormal	1	23	7	30
Blood Pressure	Normal	40	49	35	39
	High	7	6	6	26

Diabetes Mellitus category vs BP Chi-square=0.362, p=0.548. There is no association between DM and BP and ECG. Diabetic Hypothyroidism category has an association with ECG as well as BP. Chi square =9.358, p=0.002, and Chi-square=7.676, p=0.006

Table 6: Intergroup Comparison of Various Biochemical Parameters between Diabetic and Diabetic Hypothyroidism Groups

Biochemical Parameters		D	DH	P value
Sugar	FBS	160.83 ±55.41	150.51±49.74	0.16
	PPBS	233.19±77.78	216.81±52.31	0.075
Thyroid	TSH	2.18± 0.93	16.99±24.15	0
Lipid Profile	TC	167.71 ±36.10	149.43 ± 41.30	0.001
	HDL	40.51± 7.72	42.29±35.46	0.621
	LDL	105.03 ±31.52	119.28 ±42.89	0.007
	TGA	146.71 ±34.66	142.19 ±38.00	0.372

DM - Diabetes Mellitus, DMH - Diabetes Mellitus Hyperthyroidism
 D - Diabetic, DC - Diabetic Cardiovascular, DH - Diabetic Hyperthyroidism, DHC - Diabetic Hyperthyroidism Cardiovascular
 FBS - Fasting Blood Sugar, PPBS - Postprandial Blood Sugar, TSH - Thyroid Stimulating Hormone, TC - Total Cholesterol,
 HDL - High Density Lipoprotein, LDL - Low Density Lipoprotein, TGA - Triglycerides

Discussion:

Diabetic patients have a higher prevalence of thyroid disorders compared with the normal population and it has been proven in our study, as out of 208 patients, 83 patients were newly detected DM cases, in this 39 cases had hypothyroidism and out of 39 patients, 23 patients were detected to have concomitant CVDs. This shows the high prevalence DM and hypothyroidism and association of these two metabolic disorders on peripheral tissue and cardiovascular system.

Similar results were reported by a study conducted by Raghuvanshi *et al.* [7] on 40 T2DM and compared with 40 non-diabetic patients for assessing hypothyroidism and subclinical hypothyroidism. They found that prevalence of hypothyroidism and subclinical hypothyroidism was found to be 4(10.00%) and 6(15.00%) respectively, the prevalence of thyroid dysfunction was found to be higher in T2DM subjects as compared to non-diabetic subjects [7].

Since thyroid disorders and DM have a common autoimmune etiology, diabetic patients having increased serum TSH is due to immunological disturbances and many diabetic patients probably suffering from subclinical hypothyroidism which are undiagnosed. The level of TSH in our study was significantly high in DMH category than in DM category subjects and results obtained have shown that in T2DM, hypothyroidism is frequently observed. These results are in accordance with the reports of Vinu *et al.* [8], Gurjeet *et al.* [9], Swamy *et al.* [10], Suzuki *et al.* [11], Celani *et al.* [12], Demitrost *et al.* [13], Witting *et al.* [14], who in separate study found altered thyroid profile in a diabetic patient.

The time of occurrence of DM and hypothyroidism was assessed in DMH category, we

noticed that, 43 patients had DM first and hypothyroidism later, 34 had hypothyroidism first and DM later, whereas in 29 patients both were diagnosed at same time. As both are metabolic disorders, so each one has influence on another and patient suffering from one metabolic disorder have more chances of developing another type of metabolic disorder and it depends on physicians treating DM patients, because only few were advised for thyroid profile and many cases were diagnosed to have hypothyroidism in our clinic.

On intracategory comparison of various laboratory parameters, in DM category, D and DC group patients had statistically significant high FBS, PPBS, LDL and lower HDL levels, whereas total cholesterol levels were high only in DC group, triglycerides and serum TSH were not significant, the dyslipidemia is known factor in uncontrolled DM patients and it worsens cardiovascular risk due to the peculiar atherogenic profile [7].

In DMH category patients had higher levels of FBS, serum TSH, total cholesterol, triglycerides, LDL and lower level of HDL and were statistically highly significant. Thyroid hormones exert profound effects in the regulation of glucose homeostasis by modifying circulating insulin levels and counter-regulatory hormones, intestinal absorption, hepatic production and peripheral tissues (fat and muscle) uptake of glucose and they oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis shown by Raboudi *et al.* [16]. Recent evidence that mild TSH abnormalities are associated not only with traditional coronary risk factors but also with mortality for coronary artery disease, support the hypothesis that even a mild reduction in TH levels plays an important role in the myocardial response

to acute ischemia [17]. On intercategory comparison there was statistical significance was observed with serum TSH, total cholesterol and LDL, this was correlated with the studies conducted by Gurujeeth *et al.* [9]; Islam *et al.* [17]; Radaideh *et al.* [18].

The clinical parameters such as ECG and blood pressure in patients of DMH category out of 106 patients, 65 (31.25%) had various CVDs, This observation is partly related to the hyperlipidemia known to be present in patients with both primary and secondary hypothyroidism [19], so high BP and ECG changes are expected in DMH patients. This gives an idea about importance of evaluation of BP and ECG before any stress inducing dental procedures in patients suffering from DM with associated hypothyroidism, as they may also be suffering from CVDs and can have serious life threatening complications. In none of the previous studies, these parameters were considered, as the coexistence of DM and hypothyroidism increase the risk of developing macrovascular complications (myocardial infarction, stroke) on the dental chair.

DM influences thyroid hormone profile, thyroid disease influences control of DM as hypothyroid

patients tend have higher FBS levels. Both diseases independently and together contribute towards dyslipidemia, low grade inflammation and atherosclerosis, thus there is a much higher cardiovascular morbidity and mortality in diabetic patients who have hypothyroidism, in such patients there is a definite risk of cardiovascular complications on the dental chair. This is further complicated by a fact that patients with DM and hypothyroidism are often asymptomatic; this study highlights the importance of assessment of thyroid status in T2DM patients.

Conclusion:

Thyroid hormones virtually affect every anatomic and physiologic component of the cardiovascular system and the classical risk factors for the development of CVD in subjects with diabetes are the presence of poor glycemic control, dyslipidemia, and hypertension. The ability to diagnose and treat unsuspected hypothyroidism in T2DM patients may greatly enhance quality of life and when patient report us for dental treatment, if we advise for such blood investigations, may help the patient and can avoid life threatening complications during invasive dental procedures.

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